420 Rec'd PCT/PTO 30 NOV 1999

FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **4068-0002-0 PCT**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): 09/424247

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/BE98/00064	**07 MAY 1998**	**07 MAY 1997**

TITLE OF INVENTION

DRY POWDER INHALER EXCIPIENT, PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

APPLICANT(S) FOR DO/EO/US

Francis VANDERBIST, et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

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01 FC:102 130.00 CH

Notice of Priority
PCT/IB/304
PCT/IB/308
Request For Consideration of Documents Cited in International Search Report
Petition to Revive an Unintentionally Abandoned Application Under 37 C.F.R. 1.137(b)
Petition to Accept Declaration Under 37 C.F.R. 1.47(a)

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09/424247	PCT/BE98/00064	4068-0002-0 PCT

20. The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☒ Search Report has been prepared by the EPO or JPO **$840.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) **$670.00**	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$760.00**	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO **$970.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$96.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	15 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☒	**$260.00**	
	TOTAL OF ABOVE CALCULATIONS		=	**$1,100.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐	**$0.00**	
	SUBTOTAL		=	**$1,100.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
	TOTAL NATIONAL FEE		=	**$1,100.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**	
Petition to Revive $1210.00	**TOTAL FEES ENCLOSED**		=	$2310.00	
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of **$2,310.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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24,618
REGISTRATION NUMBER

November 29, 1999
DATE

"Dry powder inhaler excipient, process for its preparation and pharmaceutical compositions containing it"

The present invention relates to a new pharmaceutical excipient which may be used in the formulation of dry powder inhaler compositions, to process for its preparation and to the so formulated pharmaceutical compositions.

The administration of active ingredients by inhalation has been used and recognised as a valuable technique for many years. Since the drug acts directly on the target organ, much smaller quantities of the active ingredient (when compared with oral route) may be used for obtaining the same activity, with at least the same duration of action and much fewer side effects due to the systemic absorption.

The three delivery systems available for allowing a pulmonary administration are nebulizers, pressurized metered dose inhalers (PMDIs) and dry powder inhalers (DPIs).

Nebulizers are effective but expensive, bulky and require a relatively long time of administration. As a result, they are mainly used in hospitals.

PMDIs were from far the most popular inhalation systems in the last two decades but present several disadvantages. They require a good coordination between actuation and inhalation what can be difficult for some patients. The respirable fraction that they allow to obtain is quite low (about 10 %). And last but not least, their destructive effect on the ozone layer will led in a very close future to their complete removing.

Now are appearing the first CFCs free PMDIs containing HFAs gases (hydrofluoroalkanes).

A variety of DPIs have been developed in the past few years and since DPIs rely on the inspiratory effort of the patient to produce a fine cloud of drug particles, the coordination problem associated with the use of MDIs does not apply. But, consequently, the quantity of the drug deposited in the lungs is dependent on the airflow. This dependence must be as low as possible for instance by improving the aerodynamic properties of the device and/or the quality of the formulation. There are two main kinds of DPIs (I) monodose DPIs in which the doses of active ingredient (mixed or not with an excipient) are preseparated by filling in individual gelatine capsules and (ii) multidose DPIs in which the drug (mixed or not with an excipient) is filled into a reservoir, the amount of drug delivered per actuation being controlled by a dosing chamber. A DPI's formulation typically presents a contradiction. Indeed, it is usually considered that for reaching the lungs, particle size must be smaller than 6 micrometers and to reach the deep regions of the lungs (bronchioles and alveoles), particle size must be smaller than 2 micrometers. Such micronized powders are very cohesive due to the numerous interparticles interactions occurring between them. This may cause an unreproducible filling of the gelatine capsules and/or incomplete output of the drug from the device. This is the reason why the active ingredient is either pelletized or mixed with a coarse excipient.

The lung deposition of a drug administered with a dry powder inhaler (DPI) is influenced by three kinds of parameters: the patient, the device and the formulation. Concerning the patient, the formulator must guarantee that the category of patients targeted will have a sufficient respiratory capacity to reach the wished amount of drug in the lung. Furthermore, the inhalation system has to be simple to use for allowing a good compliance from the patient. Nevertheless the patient

must be duly trained to the inhalation technique. The choice of the inhalation device is of course important. The ideal device will be simple to use, portable, cheap, multidose, must allow to obtain a high respiratory fraction in a reproducible way, must possess a protecting system against an eventual overdosage, must be as low as possible dependent on the inhalation flow. It is clear that ideally each formulation must be optimized in function of the nature and the amount of active ingredient, the device and the category of patients targeted. The formulator has several parameters to play on for optimizing the formulation. The first condition for obtaining a high lung deposition is to possess a powder with a high percentage of respirable particles. The parameters influencing the lung deposition are the following: nature, size, shape and surface properties of the carrier particles, ratio between the active ingredient and the carrier, total amount in the capsule or in the dosing chamber, humidity and electrostatic forces. The physical characteristics of the excipient are from far the most important factor. Usually an inert water soluble, free flowing, coarse excipient is used as carrier. Most often, α-lactose is used but other mono- or disaccharides may be used. The principal interest of adding this excipient is to increase the flowability of the powder. Indeed, the micronized powders present a high number of interparticular interactions and are consequently very cohesive what can provoke a bad capsule filling in case of monodose devices, a bad output of the drug from the device due to the cohesiveness of the powder or a too low respiratory fraction due to the formation of agglomerates of active ingredients which are no more able to reach the lungs due to their too large dimensions. On the other hand, the bond between the carrier and the drug must be reversible during the inhalation for allowing the redispersion of the respirable active particles. This redispersion ideally occurs within the inhaler before the penetration in the mouth and is caused by the high turbulences created into the

device by the patient's inhalation. Once the drug and the carrier are separated, their deposition in the different sites of the respiratory tract will depend on their size and mass and will be governed by inertial phenomenons. Ideally, excipient particles must deposite in the oro-pharyngeal region while the higher fraction possible of the drug must reach the deep lungs.

The most important parameters of for example α-lactose grains are the nature, the size, the flowability (Hausner ratio or angle of repose) and the rugosity which play a role in the strength of the bond between α-lactose and drug.

As it is well known, the surface characteristics of individual particles of the excipient may be modified by such conventional techniques as crystallization, spray drying and precipitation. For that purpose, patent application WO n° 91/11179 is directed to crystalline sugars such as α-lactose comprising particles having a rugosity of less than 1.75, which are useful in dry powder inhaler compositions. However, these crystalline excipients do not bind the active ingredient sufficiently strongly and generally give a mixture which is not stable and which segregates during handling and filling. On the contrary, the conventional excipients the rugosity of which is greater than 2.0, and particularly spray dried α-lactose monohydrate the rugosity of which is comprised between 2.4 and 2.8, may provoke a partially irreversible bond with the pharmaceutically active material with which it is formulated.

One of the aims of the present invention is consequently to overcome the above-mentioned drawbacks and to provide a novel form of particulate pharmaceutical excipient suitable for use in dry powder inhaler compositions, as polyvalent as possible allowing to obtain a high dose of the active ingredient in the lungs with a low variation between the inhalation device and the patients.

To this end, according to the invention, the excipient comprises a particulate roller-dried anhydrous β-lactose.

Advantageously, the roller-dried β-lactose particles have a size between 50 and 250 micrometers, preferably between 100 and 160 micrometers, and a rugosity comprised between 1.9 and 2.4.

It is also an object of the present invention to provide a process for preparing said roller-dried β-lactose excipient as well as the dry powder inhaler compositions obtained by mixing any suitable active ingredient or pharmacological agent with such particulate roller-dried β-lactose.

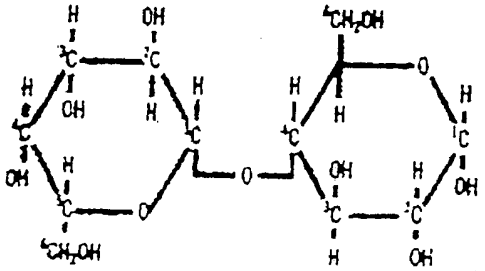
Further details and features of the invention will be evident from the detailed description given below of several particular embodiments of the invention.

As has already indicated above, the present invention mainly relates to the nature of the lactose particles used as excipient in the formulation of dry powder inhaler compositions and to the so obtained pharmaceutical compositions.

This lactose is an anhydrous roller-dried β-lactose, which is usually specifically used for direct compression and wet granulation thanks to its ability of being fragmented during compression so forming a high potential binding surface area. Such a form of β-lactose is for example obtained from DMV International under the trade designation Pharmatose DCL 21.

The structural formula of lactose is given hereinunder :

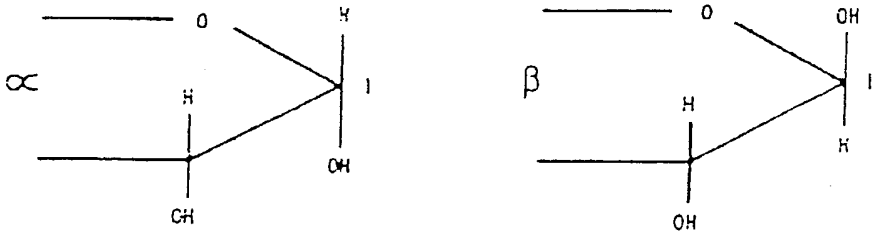
Structural formula of α-lactose



β -D-Galactose α -D-Glucose

As shown hereinbelow, the differences between the two isomeric forms α and β rely on the configuration of the hydroxyl group on the glucose molecule;

Forms of α and β lactose showing the glucose residue



Each form exist in a crystalline state α as a monohydrate and β anhydrous (plus an amorphous form which is a mixture of α and β). In aqueous solution α and β exist in equilibrium containing approximately 63 % of the β form.

Following the conditions of crystallisation, it will be obtained less or more of the α or of the β form. For obtaining a maximum of β form, all the crystallization has to be done above 93.5 °C.

The β-lactose used in the present invention is roller-dried. It is actually a lactose manufactured by the classical way including at least

the following steps: evaporation - crystallisation - separation - washing-drying - sieving. But, once the lactose is produced in a powder form, it is redissolved in demineralised water, fed between two counterrotating drums, which are steam heated. The dried lactose is then screeped from the surface of the drums by knives. This particular type of lactose provides adequate surface properties for being used in dry powder inhaler formulations, e.g. able to form reversible bonds with pharmacological active ingredients. So this invention consist first of all in the use of a type of lactose, usually reserved for wet granulation and direct compression, for DPI formulations.

It must also be noted that the low water content of anhydrous β-lactose (< 1 %) compared to α-lactose monohydrate may be particularly advantageous when the active ingredient is highly hygroscopic and sensitive to moisture even if this molecule of water is an integrating part of the lactose molecule and is not easily released at low temperature. Examples of pharmacological agents which can be usefully mixed with the roller-dried β-lactose are the mucolytics, steroids, sympathomimetics, proteins, peptides and inhibitors of mediator's release. A specific example of mucolytic substance which may be used in the preparation of DPI compositions of the present invention is the L-lysine N-acetylcysteinate. L-lysine N-acetylcysteinate is a mucolytic and antioxidant drug presenting interesting properties in chronic lung diseases with hypertension like cystic fibrosis and chronic obstructive pulmonary disease. As is it well known, the active ingredient will be a particulate solid with a particle diameter preferably comprised between 0.5 and 6 micrometers in order to obtain a high lung deposition of it.

While not wishing to be bound by any theory, the fact that the roller-dried anhydrous β-lactose gives better results than the conventional α-lactose excipients, and more particularly than the spray-

dried monohydrate α-lactose could be explained by more adequate surface properties for the roller-dried β-lactose which allows to obtain adequate binding forces between the drug and the excipient or carrier. These binding forces are essentially governed by the surface roughness (rugosity) of excipient particles. This rugosity is defined as the ratio between the surface area (derived from air permeability) to the theoretical external surface (assuming that all particles are spherical). Indeed the excipient must bind the active ingredient sufficiently strongly for allowing to obtain a stable and homogeneous mix which does not segregate during handling and filling. On the other hand, the link between drug and excipient may not be too strong in order that the individual drug particles may be redispersed during inhalation. Contrary to the above-mentioned patent application WO n° 91/11179 which describes the use of a recrystallized α-lactose of very low rugosity (1.75), the anhydrous roller- dried β-lactose used according to the present invention has a relatively high rugosity comprised between 1.9 and 2.4 This value is however inferior to this obtained with spray-dried α-lactose monohydrate which is comprised between 2.4 and 2.8. As already mentioned the higher rugosity of spray-dried α-lactose compared with roller-dried β-lactose may provoke a partially irreversible bond between lactose and drug, what may explain the lower lung deposition results of the spray-dried α-lactose monohydrate compared to the roller-dried anhydrous β-lactose, as it will be exemplified hereinafter.

As also indicated earlier the roller-dried β-lactose particles have preferably a size within the range of 50 to 250 micrometers and more preferably within the range of 100 to 160 micrometers.

The weight ratio of active ingredient to β-lactose excipient may vary depending upon the active ingredient used and in terms of its degree of activity. The optimum ratio will depend also upon the nature of

the drug. In any way, it has been found that the use of weight ratios of active ingredient in relation to β-lactose excipient of from 0.1/100 to 50/100, provides satisfactory results.

The invention will now be illustrated in further detail by the following non-limitating Examples.

Example 1

For proving its usefulness in dry powder formulations for inhalation, the roller-dried anhydrous β-lactose was compared with (i) a 325 mesh monohydrate crystalline α-lactose (which is the lactose usually used for DPI formulations), (ii) a coarser monohydrate crystalline α-lactose and (iii) a coarser spray-dried hydrous α-lactose. For this purpose, a formulation of 6 mg of L-lysine N-acetyl cysteinate (NAL) and 24 mg of the different lactose types were done and assessed in vitro on the 2 stages Twin Impinger at 60 l/min. The device used was the monodose Miat Inhaler

Both the spray-dried and the roller dried lactose were found to be superior in term of deposition than was the crystalline α-lactose probably because of more adequate surface properties. The results are shown in Table 1.

Table 1

In vitro deposition study (TI, 60 l/min.) with different lactose types using a 1:4 NAL/lactose mixture (30 mg of mixture/capsule). Three capsules / test (= 18 mg of NAL). Each result is the mean of 5 reproducible tests (n=5).

	α-Lactose crystalline (325 mesh)	α-Lactose crystalline (63-100 µm)	Spray-dried α-lactose monohydrate (63-100 µm)	Roller-dried β-lactose anhydrous (63-100 µm)
DEVICE (mg)	6.3 ± 1.4	5.1 ± 1.2	4.9 ± 0.9	5.6 ± 1.2
UPPER STAGE (mg)	4.6 ± 1.2	5.8 ± 1.6	6.2 ± 1.4	5.8 ± 1.4
LOWER STAGE (mg)	3.2 ± 0.6	5.2 ± 1.1	5.5 ± 0.8	5.9 ± 0.7
% RECOVERED	78 ± 8	89 ± 9	92 + 11	96.1 ± 12
PULMONARY FRACTION (%)	17 ± 3	29 ± 4	31 ± 6	33 ± 5

Example 2

For founding the optimal granulometric range of lactose particles, three size (63-90 µm, 90-125 µm and 100-160 µm) ranges were assessed in vitro (TI) with both spray-dried and roller dried lactose. For this purpose, the various lactose were sieved twice successively on the appropriate sieves and the granulometric distribution was checked using the laser diffraction analysis (Mastersizer X, Malvern). The respiratory fraction increases with the excipient size. The roller-dried lactose of 100-160 µm was found to be the best excipient for NAL. The results are shown in Table 2.

Table 2

Influence of the nature and the size of the lactose particles on the in vitro deposition of NAL (TI at 60 l/min.).
The ratio NAL / lactose (1:4) was the same for each lactose tested and 30 mg of powder was filled into capsule.
(1 capsule / test). Each result is the mean ± SD of 3 values (n = 3).

	Spray-dried α-lactose monohydrate			Roller-dried β-lactose anhydrous		
	63-100 µm	90-125 µm	100-160 µm	63-100 µm	90-125 µm	100-160 µm
DEVICE (mg)	1.4 ± 0.4	1.7 ± 0.4	1.6 ± 0.2	1.6 ± 0.3	1.7 ± 0.5	1.6 ± 0.6
UPPER STAGE (mg)	2.0 ± 0.6	1.8 ± 0.5	2.00 ± 0.7	1.9 ± 0.6	1.6 ± 0.3	1.4 ± 0.2
LOWER STAGE (mg)	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.6	2.1 ± 0.5	2.3 ± 0.6	2.5 ± 0.4
% RECOVERED	85 ± 8	86 ± 7	88 ± 10	92 ± 5	94 ± 8	91 ± 8
PULMONARY FRACTION (%)	28 ± 4	28 ± 5	28 ± 3	35 ± 4	39 ± 2	42 ± 3

The fact that the granulometric range of 100-160 µm has given the best results in term of deposition may be explained by the differences in flowability (represented by the Hausner ratio) between the various size ranges of lactose tested as described in Table 3. The coarsest the lactose (in the range tested), the best is the flowability (and the lowest is the Hausner ratio).

Table 3

Granulometric range of roller-dried anhydrous β-lactose (µm)	Hausner ratio
125-160	1.14
90-125	1.16
75-90	1.33
63-75	1.49

Another advantage of using a coarse excipient in DPI formulations is that practically no lactose may reach the lungs in this case. Indeed, when the formulations using 63-90, 90-125 or 100-160 µm lactose are tested in vitro on the two stages Twin Impinger at 60 L/min, no lactose is detectable on the lower stage of the TI, while when conventional lactose of 325 mesh is tested in the same conditions, between 1 to 5 % of lactose is able to reach the lower stage of the TI. This lung deposition of lactose may be responsible for some irritants effects of DPI formulations.

Example 3

The last parameter to optimize is the ratio between drug and β-lactose. Mixtures of NAL/β-lactose were realized from 1:2 to 1:6 (higher dilutions were not realistic because the therapeutical lung dose of NAL could not be reached) and assessed on the 2 stages Twin

Impinger using 30 mg of powder for each mixture. Mixtures from 1:2 to 1:4 were found to give the best results. The mixture 1:4 is definitely considered as the best as it is the only one who allows to obtain a high respirable fraction with keeping an acceptable flowability. The results are indicated in Table 4.

Table 4

Influence of the ratio NAL/β-lactose on the in vitro deposition of NAL (TI, 60 l/min.).

For each mixture 30 mg of powder was filled into capsule and each result presented is the mean ± SD of 3 values (n = 3).

The lactose used was the roller-dried β-lactose anhydrous of 100-160 µm (1 capsule / test).

	NAL/lactose 1:2	NAL/lactose 1:3	NAL/lactose 1:4	NAL/lactose 1:5	NAL/lactose 1:6
DEVICE (mg)	3.4 ± 1.0	2.5 ± 0.4	1.7 ± 0.3	1.6 ± 0.5	1.1 ± 0.4
UPPER STAGE (mg)	2.6 ± 0.9	1.7 ± 0.4	1.5 ± 0.5	1.5 ± 0.3	1.1 ± 0.4
LOWER STAGE (mg)	3.3 ± 1.1	2.5 ± 0.6	2.1 ± 0.5	1.0 ± 0.2	0.9 ± 0.2
% RECOVERED	95 ± 9	89 ± 7	88 ± 6	81 ± 10	71 ± 8
PULMONARY FRACTION (%)	35 ± 6	33 ± 5	32 ± 4	19 ± 3	22 ± 5

Electron micrographs of a selection of the above powders are shown in the accompanying Figures. In Figures 2 and 3, the magnification and an approximate scale is given.

Figure 1 represents a picture taken by scanning electron microscopy (SEM) of a) the spray-dried α-lactose monohydrate and b) the roller-dried anhydrous β-lactose. It is well visible that there are significative differences between both types of lactose. The roller-dried β-lactose particles are less spherical and show a slightly smoother surface than the spray-dried lactose (what is a visual confirmation of the rugosity measurement).

Figure 2 shows a picture taken by SEM of a grain of the roller-dried anhydrous β-lactose recovered by micronized particles of NAL.

Figure 3 represents a wider view of the picture of Figure 2. The mapping of the sulphur atom on this picture shows to what extent NAL is well fixed on the β-lactose grains.

An in vivo depositon study has been also realized on 6 volunteers to confirm the high respirable fraction obtained with the formulation. The mean lung deposition was superior to 30% and the lung penetration of the drug was good.

All the results described hereinabove were obtained by using the monodose Miat Inhaler. For proving that this kind of formulations is relatively polyvalent and not strictly developed for one device type, some tests were performed on a multidose DPI device. The formulation used was as follows :

NAL / roller dried anhydrous β-lactose (100-160 µm) 1:4.

When tested on the TI at 60 l/min, the respirable fraction (in proportion of the nominal dose) obtained with this device was of 33 ± 3 % (n=10).

Example 4

a) Budesonide

The therapeutical dose of the corticosteroid budesonide is very low. The nominal dose usually recommended is between 200 and 400 µg. The device used in the in vitro deposition tests with budesonide is the Miat multidose inhaler. It is completely different from the monodose device used for NAL as this last was a monodose capsule system whereas the multidose inhaler is a reservoir system working with a dosing chamber for administering the required dose of active ingredient.

Budesonide was assayed using the HPLC described in the European Pharmacopoeia 3rd edition, 1997.

A mixture of budesonide with roller-dried anhydrous β-lactose (100-160 µm) was realized in the ratio 1:9. The dose emitted/puff is about 3 mg what means approximately 300 µ g of budesonide/puff. When tested at 60 L/min, the respirable fraction eg the fraction <6.8 µm in comparison with the nominal dose was of 28.7 ± 3.4 %.

The same formulation has been tested in the same conditions with another multidose device : the Clickhaler® (ML Laboratories). The respirable fraction was of 27.9 ± 4.5 %.

b) Salbutamol

Salbutamol or albuterol is a β2-agonist widely used as bronchodilatator agent in asthma and copd. The therapeutical nominal dose by inhalation is of 100-200 µg. The device used is the Miat Multidose Inhaler.

Salbutamol was assayed using a spectrophotometric method. A mixture of salbutamol with roller-dried anhydrous β-lactose

(100-160 µm) was realized in the ratio 1:19. The dose emitted / puff is about 3 mg what means approximately 150 µ g of salbutamol/puff. When tested at 60 L/min, the respirable fraction eg the fraction <6.8 µm in comparison with the nominal dose was of 31.2 ± 5.7 %.

c) **Sodium cromoglycate (SCG)**

Sodium cromoglycate is a prophylactic agent widely used in the chronic treatment of asthma. The therapeutical nominal dose usuall used is of about 20 mg.

Sodium chromoglycate was assayed using a spectrophotometric method. A mixture of micronized SCG with roller-dried anhydrous β-lactose (100-160 µm) was realized in the ratio 1:2. The Monodose Miat Inhaler was for performing the in vitro deposition tests. 60 mg of the mix (corresponding to 20 mgf of SCG) has been put into N° 3 hard gelatin capsules.

The in vitro deposition (represented by the Mass Median Aerodynamic Diameter or MMAD) of the capsules, containing a mixture of micronized sodium cromoglycate fixed on roller-dried lactose DCL21 (100-160 µm) in the ratio 1:2, has been assessed at various airflow from 40 L/min up to 100 L/min and compared with the commercial Lomudal Spincaps® (Fisons). The apparatus used for assessing the deposition is the Multistage Liquid Impringer.

Table 5 hereinbelow gives the airflow influence on the MMAD and on the pulmonary fraction (PF %) for both formulations.

Table 5

Airflow rate (L/min)	MMAD (µm) Roller-dried lactose	MMAD (µm) Lomudal Spincaps	PF % Roller-dried lactose	PF % Lomudal Spincaps
40	2.63	3.09	30.86	7.61
60	2.25	2.31	32.30	14.45
80	2.25	1.98	29.30	19.21
100	2.14	1.69	25.73	27.88

The very low dependence to the airflow presented by the formulation using roller-dried lactose guarantees that the lung deposition of SCG will be approximately the same for mild, moderately and severely ill patients (25 to 30 %) while the situation is completely different with Lomudal Spincaps. Indeed, this kind of formulation gives a lung deposition of SCG 4 times superior when teted at 100 L/min in comparison to the test at 40 L/min corresponding to a very high intra and inter subject variation. This illustrates another potential advantage of the DPI formulation using roller-dried β-anhydrous lactose.

The foregoing is merely illustrative of the invention and is not intended to limit it to the disclosed excipients, methods and compositions. Many variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

AMENDED CLAIMS

[received by the International Bureau on 20 October 1998 (20.10.98); original claims 1,2,4,10,11 and 13 amended; remaining claims unchanged (2 pages)]

1. A pharmaceutical excipient useful in the formulation of dry powder inhaler compositions, characterized in that it comprises a particulate roller-dried anhydrous β-lactose.

2. An excipient according to claim 1, characterized in that the roller-dried anhydrous β-lactose particles have a size between 50 and 250 micrometers.

3. An excipient according to claim 2, characterized in that said particles have a size comprised between 100 and 160 micrometers.

4. An excipient according to any of claims 1 to 3, characterized in that said particulate roller-dried anhydrous β-lactose has a rugosity comprised between 1.9 and 2.4.

5. A dry powder inhaler pharmaceutical composition, characterized in that it comprises a mixture of an active ingredient and an excipient as claimed in any one of claims 1 to 4.

6. A composition according to claim 5, characterized in that the active ingredient is a particulate solid with a particle diameter comprised between 0.5 and 6 micrometers.

7. A composition according to either of claims 5 and 6, characterized in that the weight ratio of the active ingredient in relation to the excipient is of from 0.1/100 to 50/100.

8. A composition according to any of claims 5 to 7, characterized in that the active ingredient is selected from the group comprising mucolytics, steroids, sympathomimetics, proteins, peptides and inhibitors of mediator's release.

9. A composition according to claim 8, characterized in that the active ingredient is a mucolytic agent such as L-lysine N-acetylcysteinate.

10. A composition according to claim 9, characterized in that it comprises a mixture of particulate L-lysine N-acetylcysteinate and

roller-dried anhydrous β-lactose constituted by particles of 100 to 160 micrometers in size and of 1.9 to 2.4 in rugosity, the weight ratio of L-lysine N-acetylcysteinate in relation to the roller-dried anhydrous β-lactose being of from 1/2 to 1/6.

11. A composition according to claim 9, characterized in that the weight ratio of L-lysine N-acéthylcysteinate in relation to the roller-dried anhydrous β-lactose is comprised between 1/2 and 1/4.

12. A composition according to claim 11, characterized in that said weight ratio is of the order of 1/4.

13. A process for the preparation of an excipient as claimed in any one of claims 1 to 4, characterized in that anhydrous β-lactose in a powder form is dissolved in demineralised water, fed between two counterrotating drums, which are steam heated and then screeped from the surface of the drums.

US005551489A

United States Patent [19]

Trofast et al.

[11] Patent Number: 5,551,489

[45] Date of Patent: Sep. 3, 1996

[54] **AGGLOMERATION OF FINELY DIVIDED POWDERS**

[75] Inventors: **Eva A. C. Trofast**; **Erik J. Falk**, both of Lund, Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[21] Appl. No.: **317,033**

[22] Filed: **Oct. 3, 1994**

[51] **Int. Cl.**[6] **B65B 1/04**; B65B 3/04

[52] **U.S. Cl.** **141/18**; 141/69; 241/76; 241/153; 209/2; 209/3; 366/221

[58] **Field of Search** 141/1, 69, 18, 141/34, 98, 286; 222/238; 241/284, 24, 29, 76, 77, 78, 153; 209/2, 3, 10; 264/15, 117; 366/220, 221, 225

[56] **References Cited**

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Assistant Examiner—Steven O. Douglas
Attorney, Agent, or Firm—Fish & Richardson P.C.

[57] **ABSTRACT**

A method and system for improving the flow properties of finely divided powders is provided. The method includes (a) agglomerating the powder by passing it through a screw feeder; and (b) spheronizing the agglomerates. The method preferably further includes (c) sizing the spheronized agglomerates. Spheronization is preferably accomplished by tumbling the agglomerates in a tilted rotating container.

26 Claims, 3 Drawing Sheets

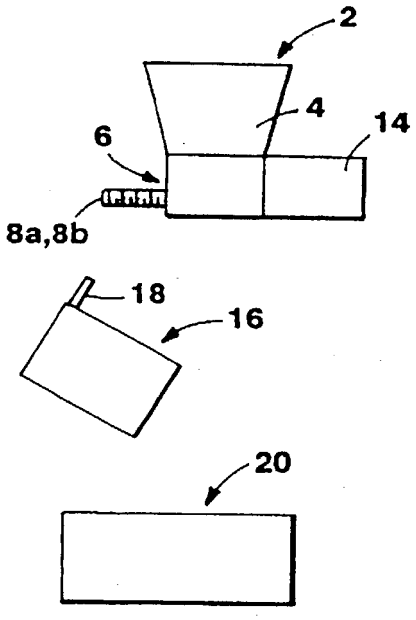


Fig. 1

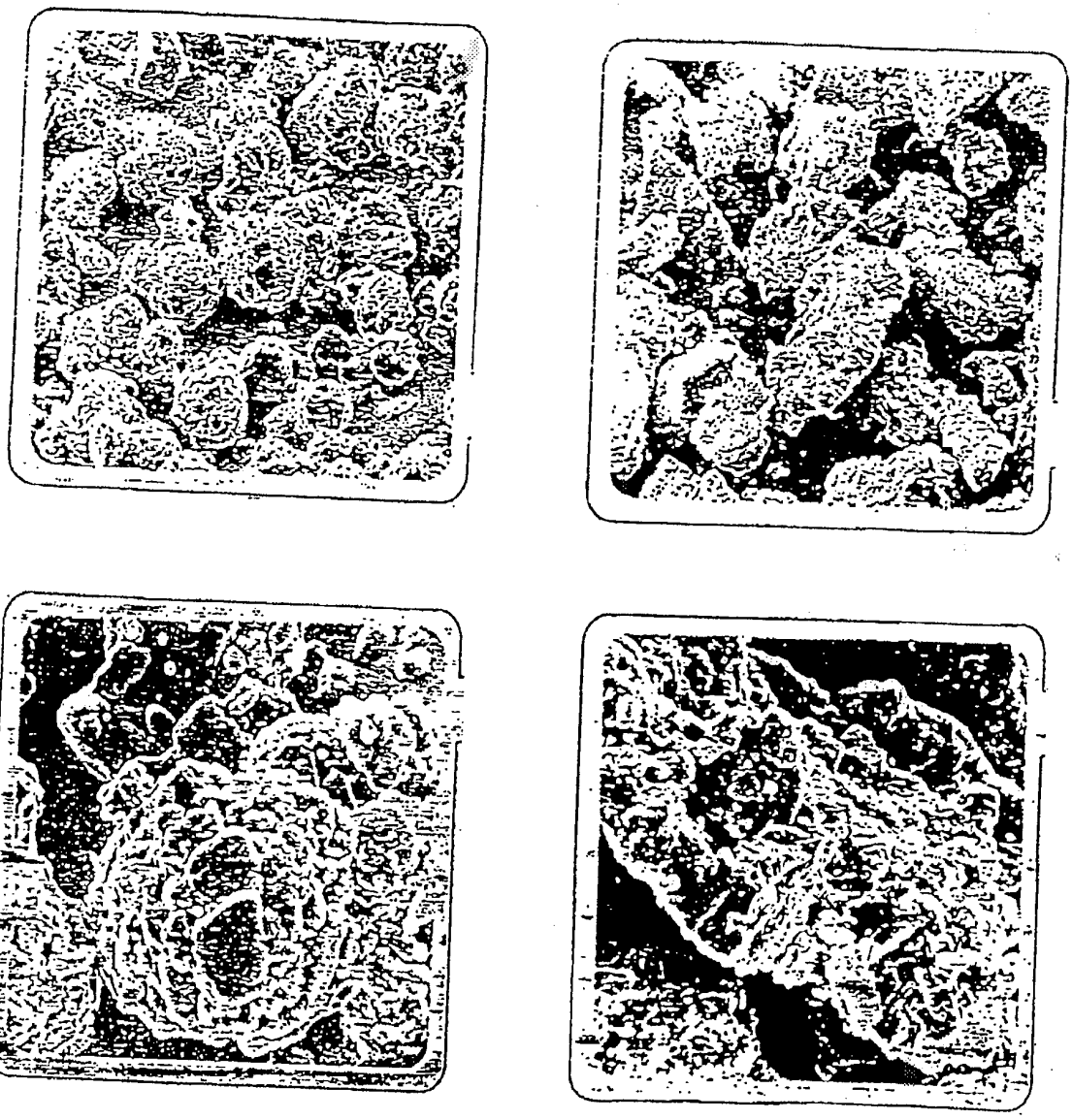
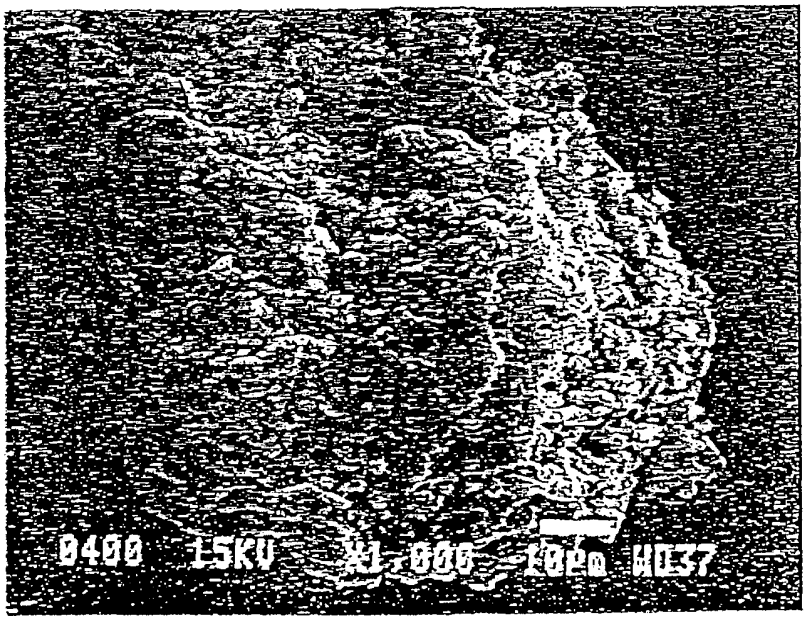


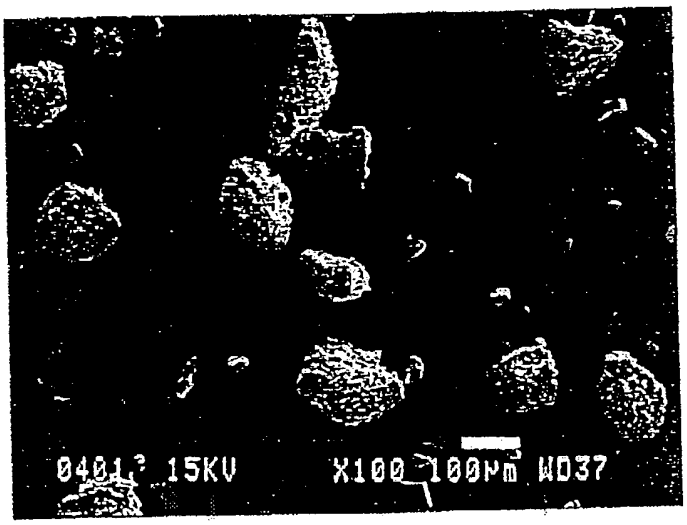
Fig. 2



10 micrometers

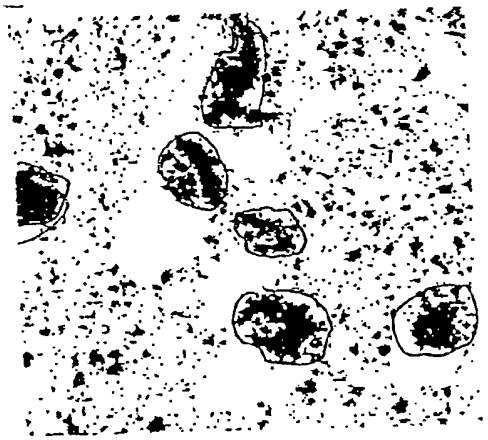
1000 X

Fig. 3



100 micrometers

100 X



Declaration and Power of Attorney For Patent Application
Declaration Pour Demandes de Brevets Avec Pouvoirs
French Language Declaration

En tant qu' inventeur nomme ci-après, Je déclare par le présent acte que:

Mon nom, mon domicile, mon adresse postale, ma nationalité sont ceux qui figurent ci-après,

Je déclare que je crois être l'inventeur original, premier et unique (si un seul nom figure sur le présent acte) ou un des co-inventeurs, originaux et premiers (si plusieurs noms figurent sur le present acte) du sujet revendiqué et pour liquel un brevet est demande sur la base de l'invention intitulée:

_____

_____

_____,

dont la description
(cocher la case correspondante)

☐ est annexée au présent acte.

☐ a été déposée _____

Numéro de série de la demande _____

et modifiée le _____.
(si approprié)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

DRY POWDER INHALER EXCIPIENT, PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT,

the specification of which

(check one)

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____.
(if applicable)

Je déclare par le présent acte avoir examiné et compris le contenu de la description identifiée ci-dessus, revendications y compris, et le cas échéant telle que modifiée par l'amendment cité plus haut.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Je reconnais le devoir de divulguer l'information qui est en rapport avec l'examen de cette demande selon Titre 37 du Code des Reglements Fédéraux §1.56(a).

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant une date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365 (b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, by checking the box, and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior foreign application(s) Demande(s) de brevet antérieure(s) (Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Année de dépôt)	Priority Not Claimed Droit de priorité non revendiqué
97870065.6	Europe	7 MAY 1997	☐
			☐

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 119(e) du Code des Etats-Unis, de toute demande de brevet provisoire effectuée aux Etats-Unis et figurant ci-dessous.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 120 du Code des Etats-Unis, de toute demande de brevet effectuée aux Etats-Unis, ou en vertu du Titre 35, § 365(c) du même Code, de toute demande internationale PCT désignant les Etats-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, § 112 du Code des Etats-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande:

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending, abandoned) (Statut) (breveté, en cours d'examen, abandonné)
PCT/BE98/00064	7 MAY 1998	

Je déclare par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique; et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la Section 1001 du Titre 18 du Code des Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

REJECTED

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POUVOIR: En tant qu'inventeur, je désigne l'(les) avocat(s) et/ou l' (les) agent(s) suivant(s) pour poursuivre la procédure de cette demande et traiter toute affaire la concernant supris du Bureau des Brevets et de Marques;

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number 25,599; Arthur I. Neustadt, Registration Number 24,854; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; Stephen G. Baxter, Registration Number 32,884; Martin M. Zoltick, Registration Number 35,745; Robert W. Hahl, Registration Number 33,893; Richard L. Treanor, Registration Number 36,379; Steven P. Weihrouch, Registration Number 32,829; John T. Goolkasian, Registration Number 26,142; Marc R. Labgold, Registration Number 34,651; William J. Healey, Registration Number 36,160; Richard L. Chinn, Registration Number 34,305; Steven E. Lipman, Registration Number 30,011; Carl E. Schlier, Registration Number 34,426; James J. Kulbaski, Registration Number 34,648; Catherine B. Richardson, Registration Number 39,007; Richard A. Neifeld, Registration Number 35,299; and J. Derek Mason, Registration Number 35,270; with full powers of substitution and revocation.

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(Supply similar information and signature for third and subsequent joint inventors.)

French Language Declaration

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Signature de l'inventeur Date	Fourth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du second co-inventeur, le cas echeant	Full name of fifth joint inventor, if any
Signature de l'inventeur Date	Fifth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du second co-inventeur, le cas echeant	Full name of sixth joint inventor, if any
Signature de l'inventeur Date	Sixth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address

(Fournier les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)

09424247 .103002

ATTORNEY DOCKET NO.: 4619-009

DECLARATION FOR PATENT APPLICATION AND APPOINTMENT OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention (Design, if applicable) entitled: **DRY POWDER INHALER EXCIPIENT, PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

the specification of which (check one):

☐ is attached hereto.

☐ was filed on November 30, 1999 as Application Serial No. 09/424,247.

☐ was filed on _____ as International Application (PCT) No. _____, and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to the examination of this application in accordance with *Title 37, Code of Federal Regulations, § 1.56*. I hereby claim foreign priority benefits under *Title 35, United States Code § 119* of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which the priority is claimed.

PRIOR FOREIGN APPLICATION(S)

NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
97870065.6	**Europe**	**7 May, 1997**	☐ Yes ☒ No
			☐ Yes ☐ No

I hereby claim the benefit under *Title 35, United States Code, § 120* of any United States application(s) or PCT international application(s) designating The United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of *Title 35, United States Code, § 112*, I acknowledge the duty to disclose material information as defined in *Title 37, Code of Federal Regulations, § 1.56* which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

APPLICATION NUMBER	FILING DATE	STATUS (Patented, Pending or Abandoned)
PCT/BE98/00064	**May 7, 1998**	**Pending**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under *Section 1001 of Title 18 of the United States Code*, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: We hereby appoint as our attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **Allan M. Lowe**, Registration Number 19,641; **Benjamin J. Hauptman**, Registration Number 29,310; **Michael G. Gilman**, Registration Number 19,114; **Kenneth M. Berner**, Registration Number 37,093; **Henry M. Zykorie**, Registration Number 27,477; **Randy A. Noranbrock**, Registration Number 42,940; and **William E. Beaumont**, Registration Number 30,996.

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I hereby authorize the U.S. attorneys and agents named herein to accept and following instructions from _____ as to any actions to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys will be so notified by the undersigned.

☒ *See following page(s) for additional joint inventors.*

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DECLARATION FOR PATENT APPLICATION AND APPOINTMENT OF ATTORNEY

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Full Name of Third Inventor: **Phillippe R. BAUDIER**	
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Residence: **Rue Engeland338, B-1180 Brussels, Belgium**	
Citizenship: **Belgium**	
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Full Name of Forth Inventor:	
Inventor's signature:	Date:
Residence:	
Citizenship:	
Post Office Address:	

Full Name of Fifth Inventor:	
Inventor's signature:	Date:
Residence:	
Citizenship:	
Post Office Address:	

Full Name of Sixth Inventor:	
Inventor's signature:	Date:
Residence:	
Citizenship:	
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